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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,899	06/04/2001	Nnochiri N. Ekwuribe	9233-54	5139

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EXAMINER

RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 06/06/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/873,899

Applicant(s)

EKWURIBE ET AL.

Examiner

Jeffrey E. Russel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 April 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 7-11, 16-30, 40, 41, 46-48, 50, 52 and 68-71 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 5) ☒ Claim(s) 16, 18-23, 25-28 and 68-70 is/are allowed.

- 6) ☒ Claim(s) 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, 52 and 71 is/are rejected.

- 7) ☒ Claim(s) 24 is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.

- 10) ☒ The drawing(s) filed on 10 October 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)

- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11, 12.

- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.

- 5) ☐ Notice of Informal Patent Application (PTO-152)

- 6) ☐ Other:

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1. Claims 30 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "the composition of claim 1" at claim 30, line 3. Note that claim 1 is drawn to a mixture, whereas claim 29 is drawn to a composition. There is no antecedent basis in the claims for the phrase "the human insulin" at claim 71, line 2. Note that claim recites "insulin" rather than "human insulin".

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-142 of copending Application No. 10/235,381. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '381 application anticipate the instant claims. Note that the '381 application claims monodispersed mixtures of an insulin drug-oligomer conjugate (see, e.g., claims 21, 45, and 67) where the oligomer can be $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 18, 24, 42, 48, 64, 70, and 71).

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-230 of copending Application No. 10/075,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '097 application anticipate the instant claims. Note that the '097 application claims monodispersed mixtures of an insulin drug-oligomer conjugate where the oligomer is $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 170, 183, and 186).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Ekwuribe et al (U.S. Pub. No. 2003/0050228). Ekwuribe et al '228 teaches and claims monodispersed mixtures of an insulin drug-oligomer conjugate where the oligomer is $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 170, 183,

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and 186). Ekwuribe et al '228 is prior art against the instant claims because its disclosure of the monodispersed mixtures is supported by the disclosure of the provisional application upon which it claims priority (see, e.g., page 9, lines 21-27, of provisional application 60/269,198) and because the inventorship of Ekwuribe et al '228 is different than the inventorship of the instant application.

7. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Radha Krishnan et al article teaches methoxy-polyethylene glycol having 7 ± 3 subunits conjugated through hexanoic acid to the amino group of the LysB29 residue of human insulin. The conjugates are orally active and thermally stable. See, e.g., Figure 1 and page 1039, column 2, last paragraph. The Radha Krishnan et al article does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-Hex-insulin conjugates of the Radha

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Krishnan et al article using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see *In re Kamlet*, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Radha Krishnan et al article; because the use of discrete length PEG in the conjugates of the Radha Krishnan et al article would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

8. Claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-3, 7-11, 17, 29, 30, 40, 41, 46-48, 50, and 52 above, and further in view of the Harris et al article (J. Macromol. Sci., Vol. C25, pages 325-373). As noted above, while the Radha Krishnan et al article does not teach the polymer size for insulin conjugates in particular, the Harris et al article teaches that when using PEG-protein conjugates, PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to optimize result-effective conjugate properties, e.g., polymer size, as taught by the Harris et al article for the PEG-insulin conjugates of the Radha Krishnan et al article in order to

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maximize the conjugates' desirable properties.

9. Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

The amendments to the claims overcame the rejections under 35 U.S.C. 112, second paragraph, and under 35 U.S.C. 103 set forth in paragraphs 1 and 7-10 of the previous Office action.

The provisional obviousness-type double patenting rejections over copending Application Nos. 09/873,797 and 09/873,731 set forth in the previous Office action are withdrawn in view of the amendments to the claims.

The Katz-type declaration by Radhakrishnan filed April 28, 2003 is not sufficient to show that the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) is not by another and therefore unavailable as prior art under 35 U.S.C. 102(a). In particular, the declaration in paragraph 3 indicates that there are four inventors of the instant application, and in paragraph 5 indicates that the authors of the article who are not inventors performed experiments under the direction and supervision of the four inventors named in paragraph 3 of the declaration. However, the instant application has five named inventors, Amy L. Oldenbaugh being the fifth named inventor. It is possible that as a result of the amendments to the claims, Inventor Oldenbaugh is no longer an inventor of the invention as is currently claimed. In this case, a petition to correct inventorship under 37 CFR 1.48(b) should be submitted, and once the petition is granted, the Katz-type declaration by Radhakrishnan filed April 28, 2003 will be sufficient to show that the Radha Krishnan et al article is not by another and is not available as prior art under 35 U.S.C. 102(a). Alternatively, it is possible that the

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Radhakrishnan declaration filed April 28, 2003 incorrectly names the inventors of the instant claimed subject matter and/or incorrectly explains the relationship between the authors of the article and the inventors of this application. In this case, a revised Katz-type declaration may be appropriate. In any event, at this time, the Radhakrishnan declaration shows that subject matter of the Radhakrishnan et al article was derived from four inventors, which is different than the inventorship of the instant application which has five inventors. Accordingly, the Radha Krishnan et al article is by another and is available as prior art against the instant claims under 35 U.S.C. 102(a).

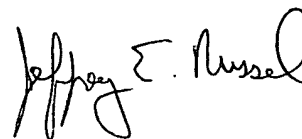
Because this application is not otherwise in condition for allowance, the provisional obviousness-type double patenting rejections set forth above can not be withdrawn in accordance with the procedures of MPEP 822.01.

10. Claims 16, 18-23, 25-28, and 68-70 are allowed. Claims 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 71 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

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JRussel

June 5, 2003